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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1653	8

DATE MAILED: 02/11/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/904,987	DOUGLAS ET AL.	
	Examiner	Art Unit	
	Samuel W Liu	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-48* is/are pending in the application.

4a) Of the above claim(s) *1-17,47 and 48* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-46* is/are rejected.

7)☒ Claim(s) *40,41 and 43-46* is/are objected to.

8)☒ Claim(s) *1-48* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *8* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

The previous Restriction Requirement mailed on 04/19/02 (Paper NO: 6) is vacated. The new restriction requirement set forth below. Examiner apologized for any inconveniences.

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-17 and 47-48 drawn to composition capable of solublizing an inappropriate folded and/or aggregated protein in the solution comprising chemical functional groups attached to the composition, buffering agents and target proteins, classified in class 546, subclass 193 and class 530, subclass 350.

II. Claims 18-46, drawn to method of *in vitro* solubilization of an inappropriate folded and/or aggregated protein and method of treating an animal by administering therapeutically effective amount of the composition capable of preventing or reversing assembly or aggregation of conformationally altered protein, classified in class 436, subclass 15 and 176, 514, subclass 228.8, and class 604, subclass 48.

The inventions are distinct each from the other because of the following reasons:

Inventions I and II are related as product and process of using the product. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed in the invention I can be used in a materially different process; picolinic acid and its analogues can be used as an anti-

virus effector (see Fernandez-Pol, J. A. *et al.* (2001) Anticancer Res. Vol. 21, 3773-3776), for example.

Additional Election

This application contains claims directed to the following patentable *distinct inventions*. The compositions solubilize inappropriate folded and/or aggregated proteins that are disease-related.

With respect to Group I, *e.g.*, Claims 2, 17 and 47 recite a structure where there are four "R"-groups (R_1, R_2, R_3 and R_4) selected from patentably distinct groups. Under 35 U.S.C. 121 as part of the response to this restriction, applicants are required to (a) select one chemical group for each of R_1, R_2, R_3 and R_4; (b) a specific cation; (c) one buffering reagent; (d) disease state affected by the claimed composition (see claim 13); (e) one sequence (see Claim 14, each sequence is physically, chemically, and biologically distinct, absent evident to the contrary); and (f) a group to which the subject protein undergoes conformational change or aggregation (see claim 13).

Note that this is not a species election but a requirement for restriction under 121 because: (1) the R-groups are different as an oligopeptide is not equivalent to a small non-peptidic organic R-group, such as $-CH_3$;

(2) each cation is different with respect to sphere of hydration as well as net charge;

(3) each buffering agent is different with respect to chemical structure and properties, e.g., fractionated vegetable oils *versus* hydroxypropyl methylcellulose (Claim 7).

(4) each disease is different with different modes of treatment and expected outcomes and

(5) each peptide is different, as for example SEQ ID No.1 has 43 residues whereas SEQ

ID NO. 2 has 77 residues.

(6) each group selected from Claim 43 is different species.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art because of their recognized divergent subject matter, or/and as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Kenneth Solomon on 30 January 2002, a provisional election was made without traverse to prosecute the invention of Group II, claims 18-46. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-17 and 47-48 withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Thus, claims 18-46 are pending and examined in this Office action.

Specification/Claim Objections

The disclosure is objected to because of the following informalities:

Claim 40 is object to because the claim recites non-elected claim 1. Note that, on examination purpose, the examiner incorporates the content of claim 1 into claim 40. See also claims 41 and 43-46. Te dependent claims are also included in the objection.

In claim 46, "conformational altered protein" should be changed to "conformationally altered protein".

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code in line 27, page 8. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

In page 24, line 1"BA" should be changed to "βA".

The disclosure is also object to since the specification recites GenBank accession NOs without providing the corresponding sequence identifiers *i.e.*, SEQ ID NOs (*e.g.*, see page 10, lines 12-13).

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-38, 40 and 42-46 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant is in possession of picolinic acid (AC), its analogs, or derivative defined in claim 2.

Applicant is not in possession of <u>any</u> PA analogues or derivatives which are structurally deviated from the unmodified PA structure. There is insufficient written description about the analog structure associated with function of promoting the subject protein assemble or preventing the protein aggregation. There is insufficient written description about additional representative species of the PA analogs or derivatives apart from the teaching in pages 5-6 and

claim 2 thereof with respect to R_1, R_2, R_3, R_4 modification, which can be lipio-modification, peptido-modification, even polynulcleotide-mofication *etc*. These chemical modifications at R_1, R_2, R_3, R_4 would result in unpredictable chemical property or/and biological function of the analog produced; *e.g.*, attachment of long fatty acid chain(s) to any position of R_1-R_4 would render the PA analog insoluble in water and unfold the subject protein rather than promote the protein properly folding or assembly. "PA analog" or "PA derivative" represents a genus encompassing numerous *polymer* or *non-polymer* organic molecules. One of skill in the art would reasonably conclude that the disclosure insufficiently provides a representative number of species to describe the genus that is "PA analog" or "PA derivative" though the specification has provided the description for *non-polymer* modification for R_1, R_2, R_3, R_4 groups. Thus, Applicant was not in possession of the claimed genus. *See University of California v. Eli Lilly and co. 43 USPQ2d 1398.*

Applicant has disclosed only PA and the limited PA analogs that have definitive structures set forth in claim 2; yet, the skilled artisan cannot envision all the contemplated analog or derivative possibilities recited in the instant claims. Consequently, conception cannot be achieved until a representative description of the structural and functional properties of the claimed invention has occurred, regardless of the complexity or simplicity of the synthetic method. Adequate written description requires more than a mere statement that it is part of the invention. See *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (CAFC1993). The Guidelines for the Examination of Patent Application Under the 35 U.S.C.112, ¶ 1"Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species disclosure of

relevant, identifying characteristics, *i.e.*, structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 20001, see especially page 1106 3rd column).

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the written description inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116.). Consequently, Applicant was not in possession of the instant claimed invention. See *University of California v. Eli Lilly and Co.* 43 USPQ2d 1398.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 18-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Consult

Claim 18 is indefinite in the recitation "introducing" because it is unclear as to whether or not picolinic acid actually contacts the conformationally changed protein. See also claims 19-39. Also, claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for

omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: administering picolinic acid (PA) to a subject (an animal) or/and contacting PA with the target protein that undergoes conformational change or aggregation. Further, claim 18 is indefinite as to lack of outcome of the claimed process, *e.g.*, maintaining or increasing solubility of the target protein in a chemical environment. The dependent claims are also rejected.

Claim 21 recites "biologically active subunit"; the recitation is indefinite as the "subunit" refers to one of folded protein chains that constitute a quaternary protein (*i.e.*, each subunit is arranged in oligomer). Yet, β-amyloid is a monomeric protein (SEQ ID NO:1) not a protein having quaternary structure that is composed by subunits. Thus, the recitation …*subunit* of at least one protein selected from…" is indefinite. See also claim 37.

Claim 36 recites "containing at least one protein…"; wherein the "containing" is not apparent as to whether or not the metalloprotein is a fusion protein in which the metalloprotein is a part of the fusion or the metalloprotein forms a complex with the protein having peptide sequence of one of SEQ ID NOS: 1-7. See also claims 37-38.

Claim 46 is indefinite in the recitation "treating conformational altered protein" because the recitation does not make it clear as to how and by what the protein is treated. Suggest "treating protein folding disease" or "treating a disease that causes protein conformation alteration".

Art Records

The prior art made of record and not applied to any of the rejection is considered pertinent to the current disclosure:

- Kato, K. *et al.* (US Pat. No. 5891916) teach a quinone derivatives (see column 1-2) as an anti- neurodegenerative reagent for treating disease state, *e.g.,* Alzheimer's diseases in which aggregation of proteins or enzymes, *e.g.*, β-amyloid plaques is a chief etiologic factor, implicating the role of the regent in preventing the protein aggregation. Yet, the patent does not expressly disclose use of the regent to treating protein conformational alteration and associated disorder/disease thereof.
- Alig, L. *et al.* (US Pat. No. 5378712) teach N-aroyl-alpha-amino-carboxylic acid derivative as a reagent for preventing blood platelet aggregation.

The reagents of both references have an unsaturated six-ring structure similar to picolinic acid (PA), but chemically different. More importantly, picolinic acid is a metal chelating compound and naturally occurring in mammalian cells. Thus, development of PA as an anti-aggregation molecule and an "enhancer" for protein assembly or folding would be advantageous over the compounds disclosed in the above reference patents due to its low or non-cytotoxicity as well as biodegradable. These advantages also allow the skilled artisan to develop very flexible administering means for treating a disease states associated with protein conformational alteration or/and aggregation (see parental issued US patents 6410570, 6407125, and 64106127393).

The same picolinic acid analogs or derivatives set forth in the current invention (see claim 2) have been disclosed in the US Pat NOs: 6410570, 6127393, and 6407125 for inactivating a virus containing metalloproteins, for treating virus-infectious diseases and for treating disease states, *e.g.*, lymphoma, pulmonary disease, contact dermatitis, osteosarcoma, and cancer and immune function disorders, respectively. Of them, the

process of inactivating a virus containing metalloprotein involves protein assembly of virion proteins wherein the protein assembly controlled by PA is the subject matter of the current invention. Thus, the PA analogs are applicable for PA-mediated protein assemble and aggregation mechanism.

In addition, the current invention and the disclosures of the parental applications (now the issued patents as indicated above) provide the guidance and working examples as to reversing or preventing the aggregation or improper assemble of conformationally altered proteins (*e.g.*, β-amyloid, see Examples 1-3 and Table 4) associated with the neurodegenerative disorders, *e.g.*, Alzheimer's disease, Parkinson's disease, Huntington's disease and amyotrophic lateral sclerosis, set forth in claims 46. As a representative, β-amyloid protein is set forth in the working examples, which precursor accumulates in Alzheimer's disease. PA reverses zinc-induced aggregation and denaturation of native β-amyloid (Examples 1-2) and promotes solubilization of the aggregated β-amyloid from brain tissue of patient suffering Alzheimer's disease (Example 3). The table (see page 13) provides teaching as to correlation between insoluble proteins (*e.g.*, aggregated or misassembled proteins) various disorders/diseases. Taken together, this application description establishes reduction to practice of the invention as conceived with regards to use of PA or analogs thereof to solubilize the aggregated or/and misfolded proteins caused by neurodegenerative disorders, and therapeutic use thereof.

The above are the related art to the current invention and it is examiner's position that the scope of claims is enable.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Wei Liu whose telephone number is (703) 306-3483. The examiner can normally be reached from 9:00 a.m. to 5:00 p.m. on weekdays. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Christopher Low, can be reached on 703 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703 308-4242 or 703 872-9306 (official) or 703 872-9307 (after final). Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703 305-4700.

SWL

Samuel Wei Liu, Ph.D.
January 30, 2003

KAREN COCHRANE CARLSON, PH.D
PRIMARY EXAMINER